"Synopsis of proposed Ph.D. research work"

EXPLORATION OF C-H FUNCTIONALIZATION FOR THE SYNTHESIS OF HETEROCYCLES

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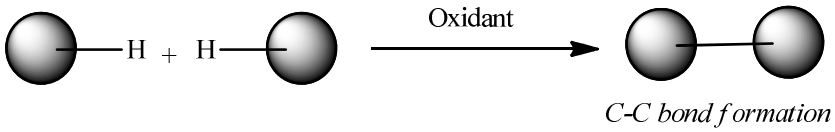
Introduction:

Heterocycles are important in organic synthesis. Direct and selective replacement of carbon-hydrogen bonds with new bonds (such as C-C, C-O, and C-N) represents an important and long-standing goal in organic chemistry.[1] These transformations have broad potential in synthesis because C-H bonds are ubiquitous in organic substances. At the same time, achieving selectivity among many different C-H bonds remains a challenge. In a broad sense, the term "C-H functionalization" (include C-H activation, C-H bond activation and C-H transformation) can be defined as the conversion of carbon-hydrogen bonds into carbon–carbon or carbon–heteroatom bonds.[2] Many definitions have been proposed by chemists from various communities (e.g., organometallic chemistry, total synthesis, or method development), thus rendering a unified definition difficult. Therefore, it is not necessarily categorize C-H functionalization reactions on the basis of the mechanism by which they occur, but rather classifies them on the basis of the net structural change engendered by the given transformation. Normally these reactions are carried out *via* classical methods such as Friedel-Crafts acylation/alkylation, oxidative phenol-phenol coupling, allylic oxidation using selenium dioxide or stoichiometric transition-metal catalysts such as chromium, and ortho- or remote metalation using stoichiometric strong bases such as alkyllithium derivatives.[3] Instead, the focus is on recent developments in C-H functionalization using transition-metal catalysis, as well as on the innovative utility of C-H bonds for the synthesis of complex organic molecules.[4] The concept of "C-H functionalization" has garnered significant attention from the synthetic community as an ideal method for the formation of carbon-carbon and carbon-heteroatom bonds, and this field has thus witnessed intensified competition.[5] Indeed, the number of publications on the topic of "C-H functionalization" has markedly increased, with more than 500 papers having been published in 2013. Early contributions in C-H functionalization were mostly reported between 1970 and 1990.[6] For example, Moritani and Fujiwara discovered the C-H alkenylation of benzene with

styrene (i.e., an alkene) in 1967 and then expanded this reaction in 1970 to the coupling between two arenes.[7] In 1982, Janowicz and Bergman demonstrated the activation of an alkane C-H bond by an oxidative addition to a transition-metal complex.[8] In 1982, Nakamura *et al*. discovered the intermolecular palladium-catalyzed C-H arylation of heteroarenes with aryl halides.[9] In 1989, Jordan and Taylor[10] demonstrated the catalytic C-H alkylation of pyridine (as an example of an electron-deficient heteroaromatic compound) and in 1993, Murai et al. discovered the ruthenium-catalyzed direct alkylation of aromatic compounds.[11] The effort of such syntheses was accompanied by the development of methods, as more practical reactions for complex molecule synthesis were deemed necessary.[12] The advent of C-H functionalization has led to the beginning of a revolution in the way one synthesizes biologically active compounds. Almost all the syntheses of natural products and pharmaceuticals that use C-H functionalization and it can be classify according to the formation of carbon-carbon or carbon–heteroatom bonds.[13] As a consequences C-H functionalization is more time efficient avoiding the multi steps and limitations associated with the preparation of functionalized starting materials and more environmentally friendly as reduces the waste formation.[14] This approach not only streamlines existing syntheses of useful molecular entities, but also contributes to changing the way of chemists thinks about chemical reactivity and plan chemical syntheses. Oxidative C-C bond formation has been achieved by various catalysts, including transition metals, organocatalysts, the combined use of metal and organocatalysts, and enzymes.[15] It is a topic that spans different modes of activation and a challenge that will continue to drive discoveries in organic chemistry.



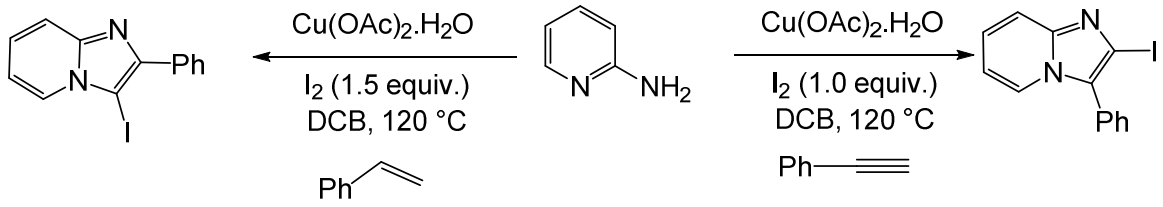
Scheme 1: C-C bond formation *via* C-H functionalization.

Objective(s) of the work:

Keeping green chemistry aspect in organic synthesis my objective is to synthesize biologically active organic molecules *via* C-H functionalization.

Methodology:

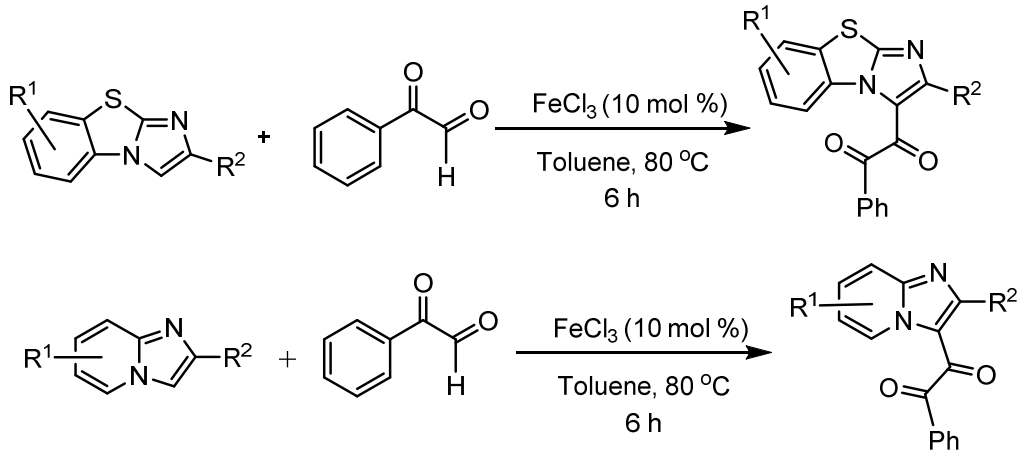
Imidazo[1,2-*a*]pyridines are the prime target of the synthetic chemists over the years due to their immense biological and pharmaceutical activities.[16] They have also applications in material science.[17] From the recent developments on the synthesis and functionalization of imidazoheterocycles, it is seen that a regio-divergent method is highly desirable that could provide both 2- and 3-iododerivatives. In continuation of our interest on imidazo[1,2-*a*]pyridines herein we report a copper-catalyzed regioselective synthesis of 2- and 3-iodoimidazo[1,2-*a*]pyridines by the coupling between 2-aminopyridine and alkenes/alkynes in presence of iodine under ambient air (Scheme 1).[18]



Scheme 1. Change of regioselectivity in the synthesis of Imidazo[1,2-a]pyridines

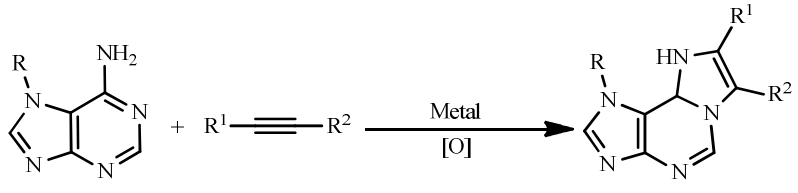
Transition-metal catalyzed C–H functionalization has become one of the fundamental methods in organic synthesis and gained a huge impact on medicinal chemistry, synthetic organic chemistry, and material science.[19] As such, advances that achieve the selective C–H bond activation for new C–C bond formation based on recently developed cross-dehydrogenative coupling (CDC) reaction have received special attention.[20] Benzo[*d*]imidazo[2,1-*b*]-thiazole and imidazo[1,2-*a*]pyridines are important fused bicyclic nitrogen containing heterocycles and have

gained much attention of the synthetic organic chemists due to their wide applications in the field of organic and biological chemistry. However, to the best of our knowledge there is no such method for the direct 1,2-dicarbonylation of imidazoheterocycles by using iron catalyst. In continuation of our research on imidazoheterocycles, herein we report a direct method for 1,2-dicarbonylation of imidazoheterocycles using phenylglyoxal through cross-dehydrogenative coupling reaction by iron catalysis (Scheme 2)

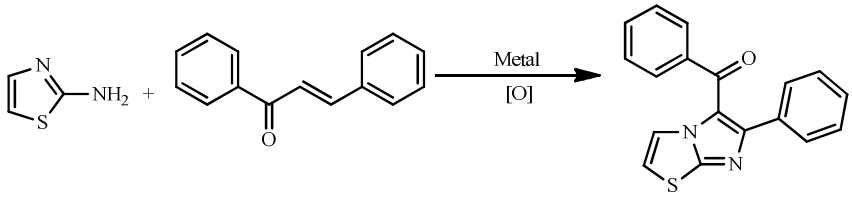


Scheme 2. 1,2-Dicarbonylation of Imidazoheterocycles

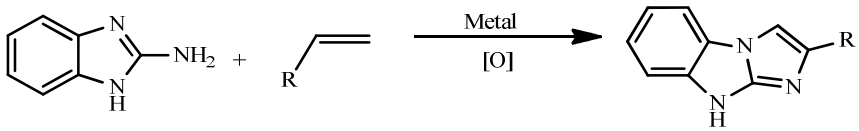
Future prospect:



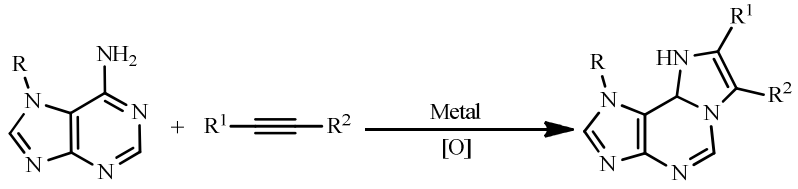
Scheme 3: Synthesis of adenine based fused heterocycles.



Scheme 4: synthesis of thiazoimidazo fused heterocycles *via* C-H functionalization.



Scheme 5: Synthesis of benzoimidazo fused heterocycles using styrene as the coupling partner.



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